REMARKS

Claim rejection under 35 U.S.C. § 112, 1st and 2nd paragraphs, and Claim Objections

Claim 19 is further clarified to render moot the rejection under section 112, second paragraph and the claim objections. The range in this claims starts from a value greater than 8.5 and goes up to a value of 9.5 (inclusive of 9.5). Thus, a value of, e.g., 11 is not included in this recited range.

Regarding the written description / new matter rejections, please consider the following.

The specification on page 5, lines 18-19, discloses that:

> In the compositions according to the invention, the pH is set within the range from 7.5 -10.5, preferably 8.5 -9.5.

Applicants are claiming a somewhat narrower range (at the low end of the range) than the literally disclosed preferred range in the application.

The courts have consistently held that an applicant disclosing a range is in possession of the invention for ranges falling within that range, i.e., is in possession of narrower ranges within the broader disclosed range.

For example, a disclosure of a 60-200°C range in a parent application was found to be adequate support for an 80-200°C range recited in a claim in a later filed application, and within the same application, a disclosure of a range of 0.6 to 1.6 mols of water in the parent application was found to be adequate support for a range of 1.2 to 1.5 mols of water in the later filed application. *In re Blaser et al.*, 556 F2d 534, 194 USPQ 122 (CCPA 1977). The Court in *In re Blaser et al.* held that the ranges in question were adequately described, and thus, the claim limitations, added by amendment, did not constitute new matter. A person skilled in the art would consider processes employing these ranges part of the invention. *In re Blaser et al., supra.* In *In re Wertheim et al.*, 541 F2d 257, 191 USPQ 90 (CCPA 1976), a solid content of 35% to 60% was found to be adequately described by a specification teaching 25% to 60% solid content. The court relying on the decisions of *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971), and *In re Smythe*, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973), held that "It is not necessary that the application describe the claim limitations exactly, but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations." The court in *In re Wertheim et al., supra*, held that a person skilled in the art would have considered processes employing

a 35% to 60% solid content range to be part of the invention, while the PTO has done nothing more than to argue lack of literal support, which is not enough because an invention claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of section 112. *In re Wertheim et al., supra.* The present situation is analogous to *In re Wertheim et al.*, and *In re Blaser et al.*. Applicants can thus properly claim a range that is narrower than that disclosed in the specification as originally filed. To hold contrary to these decisions would be contrary to well settled law.

Claim rejection under 35 U.S.C. § 103(a)

Claims 1, 2 and 4-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Odin et al (CANCER INVESTIGATION, Vol. 16 No. 7, 1998, page 447-455) in view of Beggs et al (US 5,434,087) and Nijkerk et al (WO 95/26963).

US 5,434,087 refers in its basic principle to the situation that "It would be useful to include 5'-mTHF [5-methyltetrahydrofolic acid] used in the standard reagents as a calibrator. Unfortunately, 5'-mTHF is very unstable . . ." (see column 1, lines 26-29) and later on "As mentioned earlier, there have been problems with using 5'-mTHF as a standard or calibrator. It is unstable once exposed to light, temperature and atmosphere. Its instability negates its usefulness as a calibrator." (see column 8, lines 26-29). The replacement of the instable 5-methyltetrahydrofolic acid by PGA is therefore exactly where US 5,434,087 claims to be inventive, see e.g. column 3, lines 10-13 where they state "Another advantage of the present invention is the use of PGA as a calibrator in a folate assay instead of 5'-mTHF. Traditional use of 5'-mTHF in folate assays has proved it to be an unstable compound." So in spite of having known the effect of ascorbate and citrate on the stability of 5-methyltetrahydrofolic acid, US 5,434,087 still classifies 5-methyltetrahydrofolic acid as being highly unstable and although they say that 5-methyltetrahydrofolic acid would be most useful, they classify it as unsuitable for being used as a calibrator in their folate assay.

Regarding WO 95/26963, the stabilisation of 5-formyltetrahydrofolic acid, particularly solutions thereof, cannot be compared with the stabilisation of 5,10-methylenetetrahydrofolic acid solutions. Despite belonging to the same general class of compounds (folates) the two substances show due to the methylene group in 5,10-methylenetetrahydrofolic acid, which is incorporated in a five-membered ring, properties which differ considerably. Amongst others their stability behaviour and their paths of decomposition are totally different. For a more detailed discussion on the principle of

stabilisation and the degradation pathways of 5,10-methylenetetrahydrofolic acid and of 5-formyltetrahydrofolic acid please see the reply filed on July 22, 2008.

Thus, neither secondary reference provides a reason to one of ordinary skill in the art to use citrate in the composition of Odin. For this reason alone, this rejection cannot be maintained.

Nevertheless, please consider the following. As may also be taken out of the earlier provided data is the within the present invention disclosed surprising synergistic effect of the citrate and the pH value.

Summarizing the above, the compositions of the claims demonstrate unexpected stability and represent a significant advantage over the state of the art. Additionally, one of ordinary skill in the art would not expect this behaviour of the claimed compositions because the cited publications do not teach in this direction. The claims of the present application are therefore believed to show compositions with highly unexpected attributes and, therefore, inventiveness over the references.

Claim 3 is rejected under 35 U.S.C. § 103(a) as being unpatentable over the references cited above and in further view of Cobb et al (US Patent 5,989,566).

Cobb does not cure the deficiencies of the primary references. Thus, for at least the reasons discussed above, this claim too should be patentable. Nevertheless, the following comments are provided.

The formaldehyde used in dependent claim 3 takes the role of pushing the equilibrium in between 5,10-methylenetetrahydrofolic acid on the one side and tetrahydrofolic acid together with formaldehyde on the other side into the direction of 5,10-methylenetetrahydrofolic acid. By this formaldehyde as adjuvant additionally supports the inhibition of the separation of formaldehyde (hydrolysis) from the molecule in the basic pH region. This role of formaldehyde is totally different from the role as disclosed by US 5,989,566 using formaldehyde most probably only as biological preservative for the claimed vaccine compositions.

Claim 17 is rejected under 35 U.S.C. § 103(a) as being unpatentable over the references cited above and in further view of Rabelink et al (US PGUB 2002/0052374) and Binderup (US PGPUB 2002/0183277).

Rabelink and Binderup do not cure the deficiencies of the primary references. Thus, for at least the reasons discussed above, this claim too should be patentable.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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